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Synthesis and Biological Activities of Substituted 7-Chloroquinoline Derivatives, Part II

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4,7-Dichloroquinoline was condensed with 4-aminoacetophenone to get 4-amino-(4-acetyl phenyl)-7-chloroquinoline; it was condensed with aryl aldehydes to get chalcones. The chalcones were treated with substituted hydrazines, hydroxylamine hydrochloride, urea and thiourea to get pyrazolins, isoxazolin, pyrimidine-one/thione.

4-Amino-(4-acetyl phenyl)-7-chloroquinoline, 4-amino[2-propen-1-one-1-phenyl-3-(4-methoxy phenyl)]-7-chloroquinoline, 4-amino-[3-(4-methoxy phenyl)-2-(substituted)-5-(phenyl)-3,4-dihydro-[1,5-dipyrazolin]-7-chloroquinoline, 4-amino-[3-(4-ethoxy phenyl)-5-(phenyl)-3,4-dihydro- [1,5-d]-isoxazolin]-7- chloroquinoline were prepared in this work.

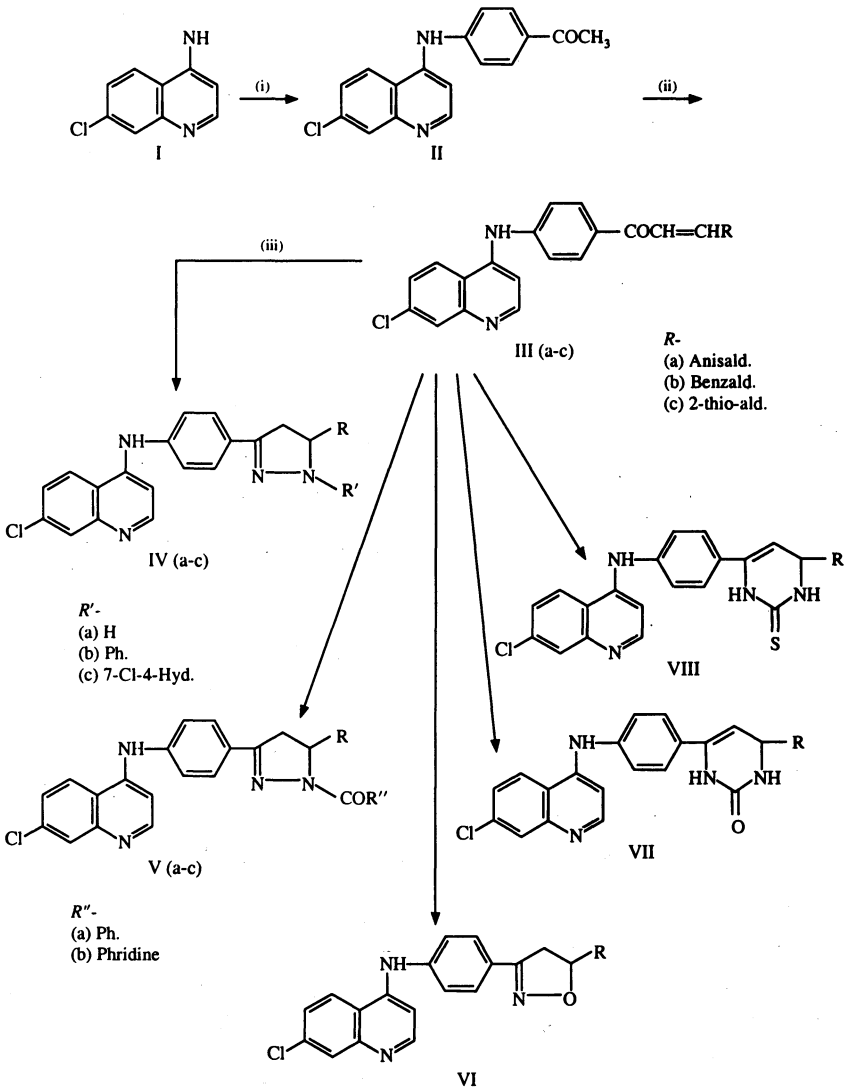
INTRODUCTION

A survey of the literature indicated that the synthesis of the new heterocyclic compounds has acquired greater importance as these compounds have a broad spectrum of antimicrobial activity. From the literature, 4-substituted quinolines were well known for their antimalarial activity[1]. In continuation of our studies on substituted 7-chloroquinolines[2-4] with a view to synthesise analogous compounds with possible antibacterial properties, chalcones were prepared using 4-amino(4-aceyl phenyl)-7-chloroquinoline. We were interested in the synthesis of Δ^2-pyrazolin derivatives[5], isoxazolin[5], pyrimidine-one[5] and pyrimidine-thione. Their antibacterial properties have been screeneed against different types of bacteria.

4-Amino-(4-aceyl phenyl)-7-chloroquinoline **(II)** was obtained by reaction of 4,7-dichloroquinoline[6] **(I)** and 4-aminoacetophenone. A new series of chalcones **(IIIa–c),** 4-amino[2-propen-1-one-1-phenyl-3-(4-methoxyphenyl)]-7-chloroquinoline **(IIIa),** 4-amino[2-propen-1-one-1-phenyl-3-(phenyl)]-7-chloroquinoline (IIIb) 4-amino[2-propen-1-one-1-phenyl-3-(thienyl)]-7-chloroquinoline **(IIIc)** were synthesised. When 4-amino[2-propen-1-one-1-phenyl-3-(4-methoxyphenyl)]-7-chloroquinoline **(IIIa)** was allowed to react with different hydrazines it gave 4-amino-[3-(4-methoxyphenyl)-2-(substituted)-5-(phenyl)-3,4-dihydro-[1,5–d] pyrazolin]-7-chloroquinoline **(IVa–c)**. Substituted Δ^2-pyrazolin derivatives **(Va–b)** were obtained by condensation of **IIIa** with substituted hydrazocarbonyl. When **IIIa** was allowed to react with hydroxylamine hydro-

chloride, it gave 4-amino-[3-(4-methoxyphenyl)-5-(phenyl)-3,4-dihydro [1,5–d] isoxazolin]-7-chloroquinoline **(VI)**. While tetrahydropyrimidine-one **(VII)** and tetrahydropyrimidine-thione derivative **(VIII)** were obtained by reaction of **IIIa** with urea and thiourea respectively.

Synthetic strategy has been outlined as below



(i) Amino acetophenone; (ii) Aryl aldehyde; (iii) Hydrazines; (iv) Hydrazocarbonyl (v) Hydroxylamine. HCl; (vi) Urea; (vii) Thiourea

EXPERIMENTAL

All melting points of the compounds synthesised are uncorrected. Micro-analyses of the compounds were carried out on a Colemn Inst. IR spectra (KBr) were recorded on an AMX-500 Bruker Inst. (500 MHz) using TMS as the internal standard in measuring PMR spectra. All the compounds gave satisfactory C, H and N analysis.

4-Amino-(4-acetyl phenyl)-7-chloroquinoline **(II)**: 4,7-Dichloroquinoline **(I)** (2 g, 0.01 mol) was treated with 4-aminoacetophenone (1.3 g, 0.01 mol) in dry acetone (25 mL). The solid separated out was crystallised from ethanol.

4-Amino-[2-propen-1-one-1-phenyl-3-(4-aryl)]-7-chloroquinoline **(IIIa–c)**: A mixture of **II** (3 g, 0.01 mol) and corresponding aromatic aldehyde (0.01 mol) was dissolved in ethanolic sodium hydroxide (40 mL, 10%). The reaction mixture was refluxed for 2 h. The solid separated out was crystallised from ethanol.

4-Amino-[3-(4-methoxyphenyl)-2-(substituted)-5-(phenyl)-3,4-dihydro [1,5-d] pyrazolin]-7-chloroquinoline **(IVa–c)**: A mixture of **IIIa** (0.4 g, 0.001 mol) and substituted hydrazines (0.0015 mol) in ethanol was refluxed for about 7 h on a steam bath. After completion of the reaction, the reaction mixture was cooled and the solid separated was crystallised from methanol.

4-Amino-[2-(arylcarbonyl)-3-(4-methoxyphenyl)-5-(phenyl)-3,4-dihydro [1,5-d] pyrazolin]-7-chloroquinoline **(Va–b)**: A mixture of **IIIa** (0.4 g, 0.001 mol) and corresponding alkyl hydrazocarbonyl (0.0015 mol) in ethanol were refluxed for about 7 h on a steam bath. After completion of the reaction, the reaction mixture was cooled and the solid separated was crystallised from methanol.

4-Amino-[3-(4-methoxyphenyl)-5-(phenyl)-3,4-dihydro [1,5–d] isoxazolin]-7-chloroquinoline **(VI)**: A mixture of **IIIa** (0.4 g, 0.001 mol) and hydroxylamine hydrochloride (0.1 g, 0.0015 mol) in ethanolic potassium hydroxide (0.4 g KOH in 10 mL ethanol) were heated for 8 h on a steam bath. The reaction mixture was cooled and poured into ice-cold water. The solid separated out was crystallised from methanol.

4-Amino-[4-(4-methoxyphenyl)-6-(phenyl)-1,2,3,4-tetrahydro [5,6–d] pyrimidine-2-one]-7-chloroquinoline **(VII)**: A mixture of **IIIa** (0.4 g, 0.001 mol) and urea (0.06 g 0.001 mol) in ethanolic potassium hydroxide (0.4 g KOH in 10 mL ethanol) were refluxed for 7 h on a steam bath. The reaction mixture was cooled, the solid separated was crystallised from ethanol.

4-Amino-[4-(4-methoxyphenyl)-6-(phenyl)-1,2,3,4-tetrahydro [5,6-d] pyrimidine-2-thione]-7-chloroquinoline **(VIII)**:: A mixture of **IIIa** (0.4 g, 0.001 mol) and thiourea (0.06 g, 0.001 mol) in ethanolic potassium hydroxide (0.4 g KOH in 10 mL ethanol) was refluxed for 7 h on a steam bath. The reaction mixture was cooled, the solid separated was crystallised from ethanol.

RESULTS AND DISCUSSION

The IR spectrum of 4-amino-(4-acetyl phenyl)-7-chloroquinoline **(II)** showed absorption band in the region of 3230–3220 cm^{-1} due to —NH stretching. The carbonyl group showed the absorption band in the region of 1670–1650 cm^{-1}.

The IR spectra of chalcones **(IIIa–c)** showed absorption band in the region

3230–3210 cm^{-1} due to —NH stretching. The carbonyl group showed the absorption band in the region of 1670–1650 cm^{-1}. The PMR spectra showed a sharp singlet at δ 3.9 ppm attributed to three protons of the methoxy group and amino proton showed singlet at δ 5.9 ppm. Aromatic proton showed multiplet at δ 7.0–7.8 ppm. The singlets at δ 8.1 ppm and 8.2 ppm attributed to methylidine proton.

TABLE-1
PHYSICAL DATA OF THE PRODUCTS

Compound No.	m.p. (°C)	Colour	Yield (%)	m.f.
II	165–66	Pale yellow	88.54	$C_{17}H_{13}N_2OCl$
IIIa	242–43	Yellow	82.45	$C_{25}H_{19}N_2O_2Cl$
IIIb	232–33	Yellow	75.77	$C_{24}H_{17}N_2OCl$
IIIc	223–24	Yellow	75.77	$C_{22}H_{15}N_2OSCl$
IVa	207–08	Pale yellow	65.50	$C_{25}H_{20}N_4OCl$
IVb	185–86	Pale yellow	59.32	$C_{31}H_{24}N_4OCl$
IVc	252–53	Pale yellow	75.77	$C_{34}H_{24_2}N_5OCl$
Va	205–06	Pale yellow	66.19	$C_{32}H_{21}N_4O_2Cl$
Vb	215–17	Pale yellow	61.24	$C_{31}H_{23}N_5O_2Cl$
VI	218–20	Pale yellow	63.57	$C_{25}H_{20}N_3O_2Cl$
VII	212–13	Pale yellow	66.56	$C_{25}H_{20}N_4O_2Cl$
VIII	250–52	Pale yellow	62.16	$C_{25}H_{20}N_4OSCl$

The IR spectra of Δ^2-pyrazolin derivatives **IVa–c** showed absorption band in the region of 3250–3230 cm^{-1} due to —NH stretching. The IR spectra did not show absorption band in the region of 1670–1640 cm^{-1} due to carbonyl group present in the starting material **IIIa**, which confirms that cyclisation has taken place, whereas the IR spectra of substituted Δ^2-pyrazolin derivatives **Va–b** showed the absorption band in the region of 1680–1670 cm^{-1} due to carbonyl group of hydrazocarbonyl. Pyrazolin exhibits —C=N— stretching frequency at 1620–1600 cm^{-1}.

The isoxazolin derivative **(VI)** showed IR absorption band at 3230–3220 cm^{-1} due to —NH stretching vibration and absence of absorption band in the region of 1670–1640 cm^{-1} due to carbonyl group. Isoxazolin exibits —C=N— stretching frequency at 1620–1600 cm^{-1}.

The IR spectra of pyrimidine-2-one derivative **(VII)** showed absorption band at 3220–3210 cm^{-1}, attributed to the —NH stretching frequency. The cyclic carbonyl group showed the absorption in the region of 1680–1670 cm^{-1}.

The IR spectrum of pyrimidine-2-thione derivative **(VIII)** showed absorption band at 3220–3210 cm^{-1} due to —NH stretching. A moderately strong band at 1445–1430 cm^{-1} in the spectra was attributed to the —C=S stretching. The PMR spectra show a sharp singlet at δ 3.9 ppm due to three protons of methoxy group. Aromatic proton showed multiplet at δ 7.0–7.8 ppm, the two amino protons showed singlets at δ 8.7 ppm and δ 8.8 ppm each.

Antibacterial activity

All the compounds were subjected to MIC (Minimum Inhibitory Concentration) Test. The stains of the following bacteria were used: *Staphylococcus aureus, Escherichia coli, Salmonella typhi* and *Klebsiella pneumoniae* and none of them showed any significant antibacterial activity.

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